A Five-Year Study of Prematurity

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• To get a comprehensive picture of prematurity and neonatal death or survival, all factors on the maternal and fetal records that might be pertinent were recorded. This information, having to do with factors such as age, gravida of the mother, blood group incompatibility, period of gestation, weight at birth, type of delivery, medication and anesthesia administered to the mother, is presented in tabular form.

In the study of perinatal mortality it was noted that failure to establish normal pulmonary ventilation is the most common cause of death in the neonatal period. Maternal history of relative infertility, that is, previous abortions, stillbirths and premature deliveries, was the most impressive finding in the stillborn series.

In the follow-up study of premature infants who survived the neonatal period, 8.5 per cent were found to be severely handicapped. In four cases the handicap was due to congenital anomalies, in two others probably to infection, leaving 12 with complications possibly ascribable to prematurity. Six of these had retrolental fibroplasia as a major handicap. In seven, mental retardation was the presenting problem. Most of the handicapped children had multiple handicaps, which included spasticity, delayed motor development, strabismus, etc. The incidence of the necessity for corrective measures for feet and legs appeared relatively high.

In general, survivors compared favorably with the rest of the childhood population. Complications and twinning were associated inordinately often.

PART I

IN ORDER TO GET a comprehensive picture of prematurity as seen at Children's Hospital, San Francisco, a study of a five-year period (1948-1952) was undertaken. The work was divided into three parts. The first part consists of data collected by coding all items on the maternal and infants' charts and compiling this material into a workable form by the use of punch cards. The second part is an analysis of fatal cases, both stillborn and neonatal deaths, and the maternal and infant factors related to the outcome. The third part is a study of follow-up data on the survivors.

Children's Hospital is a general hospital for women and children. It is largely private, but Community Chest and endowment funds permit some clinic practice. A random sampling of the five-year period under study showed that 10 per cent of the maternity patients were clinic patients and 90 per cent were private. In approximately 90 per cent of the obstetrical cases, delivery was done by physicians limiting their practice to obstetrics and in the remaining 10 per cent by a limited number of general practitioners.

The nurseries for newborn babies at the hospital are under the supervision of the Department of Pediatrics and comply with the standards formulated by the American Academy of Pediatrics.

The hospital is approved for intern and resident training.

In this study, the definition of prematurity that is accepted by the American Academy of Pediatrics was used, namely, "any child under 5½ pounds or 2,500 grams regardless of the period of gestation." The Children's Bureau interprets a live-born child as one which shows any evidence of life (breathing, heart beat, or movement of voluntary muscles) after complete birth. Birth is considered complete when the child is altogether outside the body of the mother, even if the cord is uncut and the placenta attached.

In the five-year period from January 1, 1948, to December 31, 1952, there were 11,183 deliveries at Children's Hospital. Of this number, 626 were born-alive prematures, with 90 neonatal deaths (under 28 days). The rate (per cent) of premature live births was 5.6, and the rate of neonatal deaths in the premature group was 14.07 per cent. The number of survivors was 536, or 85.93 per cent. There were 97 stillborns. As a control, data were gathered on the same number of term deliveries in the same period, the records being taken at random from the hospital's archives.

The race and economic status was included in the study but the data are of no significance because of the type of hospital and the patients admitted. Generally, in the case of indigent patients, delivery is done at a county hospital.

Data on the ages of mothers are given in Table 1. There was no appreciable difference, so far as the ages of the mothers is concerned, between the total group of born-alive prematures, the neonatal fatali-

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ties, the stillborns, and the normal control group. There was only one mother under 15 and none over 45 years of age. It is in these extremes that prematurity increases. The gravida of the mothers is shown in Table 2. The rates for the three groups—total, neonatal deaths, and stillborns—varied little between groups and differed in no appreciable degree from the corresponding data on the control group, except in the last category, "Gravida over V," where the fatality rate in prematures was higher.

Table 3 gives data on the babies with respect to Rh factor and isoimmunization factor in the parents. The ratio of known "negative" to known "positive" in the group was the same as in the general population—that is, about 15 per cent of the mothers were Rh-negative.

Maternal factors in the premature cases are listed in Table 4.

Multiple births is another factor in prematurity. During the period there was one set of triplets; all three infants survived and developed normally. There were 62 sets of twins, or 124 individuals, with a mortality of 7½ sets, or 15 individuals, a death rate of 12 per cent of premature twins. (Further comments on twinning will be made in the follow-up study on survivors.)

The type of delivery of premature infants, both of the total group and the fatal cases, is given in Table 5. The number of cesarean deliveries done in a random sampling of all deliveries during the five-year period was 7.8 per cent.

The period of gestation in this series was computed from the attending physician's calculated date of delivery as given on the medical record. Table 6 gives data on that factor. Data on the weight at birth is given in Table 7. It was interesting to note that of the total 626 live-born prematures, 55 per cent were females, whereas in the fatal cases 48.9 per cent were females.

TABLE 1.—*Age of Mothers of Premature Babies

Mothers' Age Group (Years)	Babies		
	Born Alive	Fatal Cases	Stillborn
0 to 15	1	0	0
16 to 25	208	33	27
26 to 35	344	44	58
36 to 45	73	13	12
Over 45	0	0	0
Total	626	90	97

*No difference noted in control group.

TABLE 2.—*Mothers of Premature Babies Classified as to Gravida*

Gestation of Mother Gravida	Babies		
	Total	Fatal Cases	Stillborn
I	241	30	44
II	189	32	24
III	118	18	17
IV	45	3	6
V	16	4	4
Over V	13	3	2
Total	626	90	97

TABLE 3.—*Premature Babies Grouped as to Parents' Rh and Isoimmunization*

	No. Babies
Mother Rh-negative	72
Mother Rh-positive	495
Mother's Rh not recorded	59
Isoimmunization	1
Husbands of Rh-negative mothers also Rh-negative	5
Babies of Rh-negative mothers also Rh-negative	1
Babies, with Rh-negative mothers, who died (not necessarily of erythroblastosis)	10

TABLE 4.—*Conditions Associated with Prematurity*

	No. Cases
Maternal toxemia	56
Uterine and adnexal disease	54
Infections	28
Metabolic and endocrine disease	21
Renal disease	6
Vascular disease (essential hypertension)	6
Cardiac disease	5
Genital disease:	
Premature rupture of membranes	189
Premature separation of placenta	53
Placenta praevia	19
Not significant	189

TABLE 5.—*Type of Delivery of Premature Infants*

Type of Delivery		Total	Fatal Cases
Spontaneous		133*	28
Cesarean section		91†	23
Forceps		333	27
High	3		
Mid	20		
Low	310		
Breech extraction		60	11
Version		9	1
Total		626	90

*Includes 16 spontaneous breech.
†Includes 18 repeat section.

TABLE 6.—*Data on Premature Babies with Relation to Calculated Periods of Gestation*

Gestation in Weeks	Male	Female	Total	Fatal Cases	Per Cent Fatal Cases
17 to 20	0	0	0	0	0
21 to 24	3	3	6	6	100
25 to 28	14	13	27	22	81.5
29 to 32	42	37	79	30	37.9
33 to 36	106	133	239	23	9.6
27 to 40	108	137	245	7	2.8
Over 40	9	21	30	3	10
Total	282	344	626	90	

TABLE 7.—*Distribution of Prematures by Weight Groups*

Weight Groups	Male	Female	Total	Fatal Cases			Mortality Rate (Per Cent)
				Male	Female	Total	
Less than 1,000 gm. (2 lb. 4 oz.)	14	19	33	13	16	29	87.8
1,001 to 1,500 gm. (2 lb. 4 oz. to 3 lb. 4 oz.)	31	26	57	9	11	20	35.0
1,501 to 2,000 gm. (3 lb. 5 oz. to 4 lb. 5 oz.)	43	71	114	5	10	15	13.2
2,001 to 2,500 gm. (4 lb. 6 oz. to 5 lb. 8 oz.)	188	224	412	13	3	16	3.9
Unknown	6	4	10	6	4	10	100
Total	282	344	626	46	44	90	
	45%	55%		51.1%	48.9%		

TABLE 8.—*Neonatal Deaths in Relation to Premedication and Anesthesia*

A. Premedication	Number of Cases	B. Anesthesia	Number of Cases
Atropine	1	Local	7
Barbiturates	56	Spinal	36
Meperidine	18	Caudal	9
Nisentil®	5	Pentothal intravenously	3
Morphine	6	General	32
Dilaudid®	1	None	9
Paraldehyde	3		
None	9		

TABLE 9.—*Methods of Resuscitation and Number of Premature Infants Who Received Treatment*

Method	1948	1949	1950	1951	1952	Total
Mistogen	0	0	0	7*	23*	30
Airlok	0	0	12§	38§	24§	74
Bronchoscope† or laryngoscope‡	2‡	6‡	0	6†‡	0	14
Total	2	6	12	51	47	118

*1951, 3 died; 1952, 9 died; 8 also in Airlok and 4 in Mistogen and Airlok.
§1950, all died; 1951, 8 died; 1952, 8 died.
‡1948, 1 died; 1949, 3 died; 1951, 1 died.
†1951, 1 bronchoscoped.

TABLE 10.—*Data on Oxygen Therapy of Premature Infants*

Oxygen Used	No. Cases					
	1948	1949	1950	1951	1952	Total
I. High: Live	8	3	5	6	3	25
Dead	8	18	6	12	10	54
II. Medium: Live	25	40	32	25	24	146
Dead	2	6	2	5	4	19
III. Low: Live	17	40	20	26	31	134
Dead	0	1	0	1	0	2
IV. None: Live	57	38	38	41	60	234
Dead	6	3	2	1	0	12
Total	123	149	105	117	132	626

TABLE 11.—*Type of Feeding*

Type of Feeding	No. Cases					
	1948	1949	1950	1951	1952	Total
Breast milk	0	5	1	3	1	10
Cow's milk	96	91	83	87	107	464
Both (B and C)	12	32	13	10	12	79
Others	1	0	0	0	0	1
None	14	21	8	17	12	72
Total	123	149	105	117	132	626

TABLE 12.—*Premature Infants Who Received Transfusions and Iron Therapy*

Therapy for Anemia	1948	1949	1950	1951	1952	Total
Transfusion:						
Exchange	0	0	0	0	0	0
Simple	2	5	2	4	9	22
Iron per os	7	15	3	4	3	32
Iron and simple transfusion	2	3	0	0	3	8
Total	11	23	5	8	15	62

In Table 8 is given the type of medication and anesthesia used in the fatal cases. This is given without further breakdown, which would have to be individualized to be of any significance. From a pediatric point of view, the frequency with which sedation is used is impressive and worthy of scrutiny in relation to failure to expand lungs properly, the most commonly encountered cause of death in the group.

During the five-year period, various methods of resuscitation and aiding early respiratory distress were tried (Table 9). The number of laryngoscopic examinations done varied from year to year with the training and enthusiasm of the residents.

Data on oxygen therapy over the five-year period (Table 10) will be referred to again in Part III of this report dealing with follow-up of survivors.

Since many pediatricians care for the infants on a private basis, various types of food formulas were used. The hospital is provided with breast milk by the Mothers' Milk Bank, supported by the Baby Hygiene Committee of the local American Association of University Women. In only a few cases was the diet made up entirely of breast milk, for even where breast milk was used, a change to artificial feeding was usually made several days to a week or more before dismissal. Also, several physicians used some form of concentrated protein with

TABLE 13.—*Duration of Hospital Stay of Premature Babies*

Duration of Stay	1948	1949	1950	1951	1952	Total
1 hour	4	0	0	0	0	4
2 to 24 hours	8	14	2	11	9	44
25 hours to 3 days	2	9	6	6	7	30
4 to 7 days	21	29	20	24	41	135
8 to 15 days	46	34	29	29	29	167
16 to 30 days	29	39	34	33	33	168
31 to 45 days	10	17	10	8	8	53
46 to 60 days	1	5	2	1	4	13
61 to 75 days	1	2	2	3	0	8
76 to 90 days	1	0	0	1	0	2
Over 90 days	0	0	0	1	1	2
Total	123	149	105	117	132	626

TABLE 14.—*Neonatal Deaths in Various Age Groups in Present Series*

Duration of Life	1948	1949	1950	1951	1952	Total
Less than 1 hour	4	0	1	0	0	5
2 to 24 hours	8	14	2	10	9	43
25 hours to 2 days	2	6	5	6	2	21
3 to 5 days	1	5	0	2	2	10
6 to 10 days	3	2	0	0	1	6
11 to 28 days	2	1	1	1	0	5
Total deaths	20	28	9	19	14	90
Number of autopsies	9	15	9	13	7	53

the breast milk to encourage a more rapid gain in weight.

Table 12 gives data on transfusions and iron therapy for premature infants.

Data on the hospital stay of the premature infants is given in Table 13. Most survivors were dismissed in the first 30 days; very few stayed more than 45 days.

Survival time of the premature infants in this study, which will be discussed in Part II of this presentation, is shown in Table 14.

Perinatal Mortality

Part II

Of the 626 born-alive prematures during the five-year period from 1948 to 1952, 90 died in the first 28 days. There were 97 stillbirths. In addition there were seven deaths in the first year. These groups will be dealt with separately.

A. Neonatal Deaths

Of the 90 premature babies who died, 53 were subjected to autopsy.

Table 15 gives the pathological cause of death in the cases in which autopsy was done and the clinical diagnosis in the other cases. Potter[1] noted that atelectasis is not a diagnosis and that prematurity, unless the infant is pre-viable, is not a cause of death. By these criteria, there was unsatisfactory diagnosis in 25 of the 37 fatal cases in which autopsy was not done. In only five cases in which postmortem examination was done was no adequate cause of death found. The lungs in these five were atelectatic, indicating failure to inflate properly.

From the analysis, it is obvious that the chief cause of death was lack of proper pulmonary ventilation. There were thirteen with hyaline-like membrane, six with hemorrhagic pneumonia, and, in addition, four had infectious pneumonia, prenatal in origin. In four of the eight cases in which death was ascribed to trauma, there was failure to establish normal respiration. Respiratory failure was the clinical diagnosis in four of the cases in which autopsy was not done. In 18 cases in which the cause of death could not be determined, atelectasis was noted either clinically or at autopsy.

To reduce premature mortality, the problem of establishing normal ventilation must be attacked. Much has been learned about pulmonary physiology in the last few years in the study of respiratory paralysis in poliomyelitis and in the study of cardiac surgery. Great advances have also been made in anesthesiology. The principles learned need to be applied and modified for infants. In newborn babies the problems concern essential structures that are affected before they have ever functioned, such as the respiratory center and uninflated lungs. The additional factor in preventing respiration, namely obstruction within the air passages, is relatively simple to handle. Potter repeatedly empha-

TABLE 15.—*Autopsy Diagnosis and Clinical Diagnosis in Fatal Cases*

Autopsy Diagnosis	No. Cases	Clinical Diagnosis Only
Malformations	7	0
Erythroblastosis	0	0
Anoxia (placenta praevia, abruptio placenta)	6	5
Infection:		
Prenatal 4		
Postnatal 2	6	1
Trauma	8	0
Prematurity (pre-viable)	1	12
Abnormal pulmonary function	19	4
Hyaline-like membrane 13		
Hemorrhagic pneumonia 6		
Miscellaneous	1	2
Unknown (atelectasis)	5	13
Total	53	37

sized that in fetal development the lungs are ready to function early, and only in pre-viable infants is pulmonary immaturity a cause of failure to ventilate adequately. The source of trouble, therefore, must be sought in the central nervous system and in factors affecting the respiratory center. These factors are: Anoxia due to interference *in utero* with circulation, such as premature separation of the placenta or disease of the cord; trauma during delivery, such as prolonged labor, severe moulding of the head, tears of the tentorium; shock of the infant from a combination of the factors above; and, finally, oversedation from premedication of the mother and from the anesthesia.

In the study of resuscitation, several medical specialties should participate. A valuable practice at Children's Hospital has been one or two joint conferences with new house officers yearly, in which members from the three departments — obstetrics, pediatrics and anesthesia — partake, reviewing all the foregoing factors concerning resuscitation and the immediate management of the infant.

The present practice at Children's Hospital consists of emptying the infant's upper air passages of excess fluid immediately after delivery, both by gravity drainage in the old-fashioned manner and by suction as indicated. Sometimes direct laryngoscopy is used for suctioning, other times not. Use of a bronchoscope is seldom indicated and is usually more traumatic than beneficial. The stomach contents are usually removed because a baby, only partially awake and still shocked, will regurgitate and aspirate. Often, 10 or 15 cc. of fluid is obtained. There is usually no necessity to institute immediate vigorous stimulation. A little patience is generally rewarded by the infant's making some respiratory effort. If stimulation is indicated, gentle rocking imitating a rocking-bed, or pulling the hair, may be done. If this does not suffice, oxygen under positive controlled pressure by a trained person is tried, rather than mouth-to-mouth breathing. The best method of applying positive pressure to an uninflated or partially inflated lung still needs to be devised. After respiration is established, the infant is kept in an isolette with moist oxygen, and the addition of Mistogen or Alevaire is often practiced. The oxygen is always measured, is kept under 40 per cent, and is lowered or discontinued as rapidly as the baby's function improves.

The Airlok has been available since 1950. Whether or not it is of value is controversial. The previously outlined principles of clearing the air passages and emptying the stomach contents are now conceded as necessary before placement in the Airlok, although at first it was thought that the Airlok would take care of these details. Often the infant is placed in the Airlok for the positive oxygen pressure without cycling or with only a few runs of cycling for its stimulating effect, much like a "spanking." In a private hospital with a large staff, complete uniformity of practice is unattainable. However, obstetrical rounds, as well as pediatric rounds, are conducted regularly, and a monthly review of infant morbidity and mortality is held jointly by the departments. Table 9 (in Part I of this presentation) shows the extent to which these methods of resuscitation were used during the five-year period covered by the present study.

The method of delivery is another factor in survival. The hazard of hyaline-like membrane is increased with cesarean section. This must be weighed against the hazard of waiting for a normal delivery when the fetus shows signs of distress. The incidence of cesarean section in the neonatal death series was high—25.5 per cent. In the entire series of births the incidence of cesarean section was 7.8 per cent.

The frequency of premedication is also impressive (Table 8, Part I). In only 9 of the 90 cases of neonatal death was no sedation given to the mother prior to delivery. Although sedation is selected carefully as to kind, dosage and relation to stage of delivery, there are still factors to consider in its ultimate effect on the outcome. The excretion of the drug by the infants may vary greatly, depending on many factors. Actually, very little basic knowledge on this subject has been obtained. More important, however, is the effect of even a very little sedation on a respiratory center that has not yet functioned independently and on lungs that have never been inflated. In the series, general anesthesia was given in 32 cases, local, spinal or caudal in 52 and intravenous pentothal in three. If anesthesia is combined with premedication, the effect on the infant is probably enhanced.

The other factors relevant to neonatal mortality have been more successfully dealt with. Replacement transfusions for erythroblastosis, when well done, have saved many infants that formerly would have died and have spared many others from the consequences of kernicterus.

Infection poses less of a problem than formerly, but viruses may still invade a nursery. There was one episode of diarrhea during the five-year period covered by this study. Four infants died of it—three in the neonatal period of 28 days and one later. Fortunately, this infection did not spread to other nurseries, and it is the only instance of diarrhea of the newborn in Children's Hospital. Control of infection must be directed primarily toward personnel working with the infants. Stable, well trained nurses and aides who have been carefully schooled in the hazards of mild infection are the best safeguard. After a person who works in

or near the nursery has had a respiratory or an intestinal disease he ought not return to duty except with the permission of the pediatrician in charge of the nursery or a physician delegated by him. It is important to instruct the house staff in these precautions.

Twinning is an indirect cause of neonatal mortality, but, since often one of the twins survives, comments on twinning will be made in Part III of this study.

The survival rate in the present series compares favorably with that in series reported upon by other investigators. In the Children's Bureau Manual,[2] the over-all death rates by weight groups are shown as higher than those found in the series here reported upon. For example, the death rates at the New York City hospitals in 1945 (cited in the manual) compare with the rates at Children's as follows:

Locale	Weight (Grams)			
	Under 1000	1001-1500	1501-2000	2001-2500
New York	96.1	62.1	22.9	6.3
Children's	87.8	35.0	13.2	3.9

The survival time in the series here reported upon followed the pattern noted in other series, with the first few hours, or at most 48 hours, posing the greatest hazard. Deaths thereafter are often due to congenital anomalies or rare complications (Table 14, Part I).

B. Stillborns

There were 97 stillborn infants, 50 male and 47 female, during the period studied. Autopsy was done in 31 cases, as compared with autopsy in 53 of the 90 cases of neonatal death. The reason for smaller proportion of autopsies in the stillborn group is that many bodies were macerated and such extensive autolysis had taken place that autopsy could not be performed. On the other hand, more autopsies on placentas were recorded in this group. The results of the autopsies are given in Table 16.

Sixteen of the above 31 bodies subjected to autopsy were described as macerated.

Only 8 of the 97 stillborn babies were delivered by cesarean, as compared with 23 of the 90 babies who died in the neonatal period.

There were 15 Rh-negative mothers, indicating no greater influence of this factor than in the population at large. The histories of the mothers of stillborn babies were revealing. Prenatal pathologic conditions are reported in Table 17.

In 31 of the 97 cases there was a history of previous abortions, stillbirths and premature deliveries. Similar data have been noted in other studies. In a review of perinatal deaths, the frequency of relative infertility and other factors in the history, not necessarily recorded on the hospital charts, led to an impression that maternal causes are even more prevalent than statistical studies would indicate. Often, poor babies are the result of disease of some sort during pregnancy, and the infants become the responsibility of a pediatrician who is justified, therefore, in inquiring into the prenatal life of his charge.

Internists and psychiatrists might profitably be added to the group for discussion of the problems involved in relative infertility.

TABLE 16.—*Autopsy Diagnosis in Stillborn Babies*

Malformations	5
Erythroblastosis	1
Anoxia	6
Infection	1
Trauma	4
No abnormality noted, except atelectasis	14
Total	31

TABLE 17.—*Prenatal Pathologic Conditions in Cases in Which Babies Were Stillborn*

MATERNAL FACTORS	
None	47
Bleeding in early pregnancy	14
Toxemia	11
Metabolic disorders	7
Infection first trimester	5
Headache and nausea only	1
Death in utero unexplained	7
GENITAL FACTORS	
Premature separation of placenta	26
Placenta praevia	2
Marginal placenta	2
Extensive placental infarcts	15
Placental insufficiency	3
Degenerate placenta	10
Hyperplasia of placenta	1
Inflammation of placenta	7
Cord disease	6
Premature rupture of membranes	5
Hydramnios	4

TABLE 18.—*Causes of Death After the Neonatal Period*

Case	Sex	Birth Weight (lb. & oz.)		Age	Cause
1.	M	2	12	34 days	Congenital heart disease. Aspiration. Feeble.
2.	F	3	4	36 days	Infectious diarrhea (nursery epidemic).
3.	M	4	7	2½ mo.	B. coli sepsis, including meningitis.
4.	M	5	3	2½ mo.	Congenital central nervous system anomalies and meningitis.
5.	M	3	8	2½ mo.	Asphyxiation. No other details.
6.	F	4	15	1 year	Virus infection. No other details.
7.	M	4	8	1 year	Hepatitis, etiology undetermined.

C. First Year Fatalities

As was noted earlier, it was found that seven deaths had occurred after the defined neonatal period of 28 days. The causes of death and the age at which death occurred are listed in Table 18.

REFERENCES

1. Potter, E. L.: The trend of changes in causes of perinatal mortality, J.A.M.A., 156:1471-1474, Dec. 18, 1954.
2. Premature Infants—A manual for physicians. Federal Security Agency, Children's Bureau.

Follow-up Study of Premature Survivors

Part III

In the present series 536 of the 626 born-alive premature babies survived beyond the neonatal period. As a part of the study of various aspects of prematurity, a follow-up of survivors was carried out. This was done by formulating a questionnaire that would be simple to fill out by the mothers and would reveal a fairly accurate picture of the development of the child. A photograph of the child was requested. It was not expected that all the children could be reached nor was it intended to make a statistical comparison of these children with full-term babies. The aim was to get a fair sampling of the group and to detect, if possible, the areas of development most frequently affected adversely by prematurity in order that more careful attention to these conditions might be undertaken even during the stay in the nursery. Although there are good studies on growth and development of children, there are few that give the incidence of various defects at the different age levels. The number of cases of foot and leg deformities, the frequency of strabismus, the number of respiratory infections a year at different age levels — these are things on which data are not available. Pediatricians have impressions that certain defects are more common in premature than in full-term infants. The value of the present study is limited by the inability to compare with data on full-term infants, but it highlights certain aspects of prematurity that deserve further evaluation.

It was possible to get a fairly complete follow-up on 218 children, or 40.7 per cent of the 536 survivors. There were 108 males and 110 females. A picture of the child was supplied in 98 cases, and in 40 cases the replies to the questionnaire were checked with office records of one of the authors.

The large majority of premature infants on whom follow-up data were obtained were robust, healthy little individuals who, often by one year or, at the latest, two, had compensated for their prematurity.

A careful analysis of defects recorded, and a comparison of them with the findings in the maternal and infant records, was made (Tables 19 to 21).

There were seven deaths between the neonatal 28-day period and one year. (These deaths were reviewed in Part II.) No other fatalities were reported. The study of defects was made on 211 cases.

The six cases of blindness (Table 19) were due to retrolental fibroplasia. An analysis of the cases, the years they occurred, and oxygen administration is given in Table 21.

The incidence of cardiac anomalies did not seem high. There were three babies recorded as having congenital heart defects and five others mentioned as having heart murmurs. The three with congenital defects were observed periodically in the cardiac clinic at Children's Hospital. There were five children who had been in casts for feet and leg deformities, 11 had worn braces, 33 wore corrective shoes, 11 were late walkers (after 20 months) and in one congenital abnormality of the hip is recorded. There were ten operations for inguinal hernia, seven for eye corrections, seven for miscellaneous conditions, and 25 tonsillectomies. In addition there were 11 hospitalizations for miscellaneous medical conditions. Two children were noted to have had convulsions. Four had transfusions for anemia, and six minor congenital defects (such as birthmarks and stridor) were mentioned.

A special study was made of the infants with evidence of central nervous system damage (Table 20). Several had been registered in the cerebral palsy clinic or in the neurological clinic at Children's.

Although the defects recorded in the survivors studied may seem, in aggregate, somewhat imposing, only 18 children were relatively severely

TABLE 19.—*Visual Disturbances in Premature Infants*

Abnormality	Number of Cases	Per Cent
Blindness	6	2.8
Poor vision	6	2.8
Strabismus	15 (with 7 operations)	7.1
Wearing glasses	11	5.2
Consulted ophthalmologist	49	23.2

TABLE 20.—*Central Nervous System Disease in Premature Infants*

Mentally retarded		7
Mongol	1	
Arrested hydrocephalus	1	
With motor involvement	3	
Without motor involvement	2	
Hemiplegia		1
Quadriplegia		1
Paraplegia		1
Delayed motor development and congenital heart defect		1

TABLE 21.—*Analysis of Severely Handicapped Prematures*

Case and Year	Diagnosis	Sex	Birth Weight	Hospital Stay	Oxygen	Twin	Maternal Factors	Infant Factors
1. 1949	Retrolental fibroplasia	F	2 lbs. under 1,000 gm.	70 days	Probably high	Yes	Rh negative, two previous abortions	Slow to breathe
2. 1949	Retrolental fibroplasia	F	4 lbs. 1,501 to 2,000 gm.	46 days	Probably high	No	Negative	Cyanotic spells. Grunting respiration.
3. 1950	Retrolental fibroplasia	M	3 lbs. 1 oz. 1,001 to 1,500 gm.	53 days	Probably high	No	One premature expired	Slow to breathe. Atelectasis. Positive pressure oxygen. Caffeine.
4. 1950	Retrolental fibroplasia	M	4 lbs. 5 oz. 1,501 to 2,000 gm.	34 days	Probably high	Yes Other died	Negative	Poor respiration four hours
5. 1951	Retrolental fibroplasia	M	2 lbs. 7½ oz. 1,001 to 1,500 gm.	68 days	Airlok. High O_2	No	One premature death. Gastro-enteritis one week.	Low forceps
6. 1952	Retrolental fibroplasia	M	2 lbs. 7 oz. 1,001 to 1,500 gm.	3 mo. 10 days	Airlok. High O_2	No	Gravida III. Para 0. Two previous abortions.	Footling breech. Airlok 1 hour 35 min.
7. 1948	Congenital anomalies. Arrested hydrocephalus. Mentally retarded.	M	4 lbs. 15 oz. 2,000 to 2,500 gm.	10 days	None	No	Negative	Negative
8. 1950	Hemiplegia. Strabismus.	M	2 lbs. 2½ oz. Under 1,000 gm.	84 days	High O_2	No	Lost two previous pregnancies	Cyanotic, apneic at five weeks of age. Lethargy, twitching, onset of hemiplegia.
9. 1950	Paraplegia	M	5 lbs. 8 oz. 2,000 to 2,500 gm.	16 days	High O_2	No	Rh negative. Early ruptured membranes.	Atelectasis. High forceps. Paralysis lower extremities after circumcision upon return to hospital.
10. 1950	Mental retardation	M	2 lbs. 8 oz. 1,001 to 1,500 gm.	50 days	O_2 probably high	No	Gravida V. Para II. Two previous abortions.	Cyanotic intermittently for six days
11. 1950	Spastic quadriplegia. Congenital hip.	F	3 lbs. 5 oz. 1,501 to 2,000 gm.	37 days	O_2 moderate	Yes Twin died	Gravida III. Para 0. Two previous abortions.	Condition good at birth
12.*	Mental retardation. Retarded motor development.	F	3 lbs. 1 oz. 1,001 to 1,500 gm.	37 days	O_2 high	Yes	Illegitimate pregnancy. Pre-eclampsia.	Large hematoma. Caffeine stimulation. Weak cry.
13.*	Mental retardation. Delayed motor development.	F	3 lbs. 4 oz. 1,001 to 1,500 gm.	37 days	O_2 high	Yes	Illegitimate pregnancy. Pre-eclampsia.	Version breech extraction. Subdural hematoma.
14. 1951	Mental retardation. Retarded bone age. Delayed motor development. Congenital heart.	M	2 lbs. 8 oz. 1,000 to 1,500 gm.	75 days	O_2 high	Yes Other died	Negative	Congenital heart. Difficult to establish respiration.
15. 1951	Mental retardation	M	3 lbs. 8 oz. 1,501 to 2,000 gm.	40 days	O_2 high	No	Rh negative. Premature. Ruptured membranes ten days.	Two apneic episodes. Fifth day O_2 and stimulation required.
16. 1952	Congenital heart	M	3 lbs. 9 oz. 1,501 to 2,000 gm.	36 days	O_2 high. Airlok six hours.	No	Probable German measles early pregnancy	Pale and cyanotic. Difficult to start normal respiration.
17. 1952	Congenital heart. Delayed motor development.	M	4 lbs. 14 oz. 2,000 to 2,500 gm.	12 days	Airlok. O_2 low.	No	One previous lost pregnancy. Bleeding two weeks early pregnancy.	Cyanotic. Congenital heart diagnosed. Collapse, later resuscitation.
18. 1952	Mongol	F	5 lbs. 2,000 to 2,500 gm.	17 days	O_2 low	No	Negative	Negative

*Twins to each other.

handicapped—several having multiple defects. The remaining children compared favorably with the average childhood population, their defects being remediable. The severely handicapped, as here recorded, represent 8.5 per cent of survivors studied. Table 21 is an analysis of this entire group. Twelve were males and six females. The weight varied from two to five pounds. The hospital stay varied from twelve days to over three months. Five were twins; one set is in the group, the others represent the surviving member of the set. There were four with congenital anomalies, including the one mongol in the group. The cases of hemiplegia and paraplegia may have been caused by infection, which will be discussed later. This leaves 12 cases needing special inquiry.

Of the six infants with retrolental fibroplasia, four were males and two females. The birth weight varied from 2 pounds to 4.5 pounds—one was in the weight group under 1,000 grams, three in the group 1,001 to 1,500 grams, and two in the group 1,501 to 2,000 grams. Two were survivors in twin sets. All of the six had respiratory difficulty at birth of a severe degree. Two were put in the Airlok, one for 1 hour and 35 minutes. One had respiratory distress for four hours, one had cyanotic spells and grunting respiration, and one was given oxygen under positive pressure and caffeine stimulation.

The maternal histories of the children with retrolental fibroplasia were referred to. Four of the six mothers had histories of previous premature fatalities and abortions. As was previously noted (in Part II of this study) approximately one-third of the mothers of stillborn infants had a history of previous abortions and premature fatalities. One mother had a history of two previous abortions, two had had one previous premature baby who died, and one mother was Rh-negative and had had three pregnancies that terminated in abortion. Although adverse factors necessitated placing the children in an atmosphere of high oxygen, it does not necessarily follow that the oxygen alone was the toxic agent in producing retrolental fibroplasia. It is likely that multiple factors operate and that the shock and anoxia may predispose tissues to pathologic change. This is true in kernicterus. The prenatal history and the environment of the fetus, as well as the shock of delivery, should be considered in a study of etiologic factors. Genetic factors may also play a role.

The six children with severe brain damage, but without retrolental fibroplasia, varied in weight at birth from 2 pounds 8 ounces to 3.5 pounds. Two were a twin set, and two others were survivors of twins. Four of the six had high oxygen therapy.

The size of the infant is not the sole determining factor, for although nine premature babies from the nursery at Children's Hospital have registered in the cerebral palsy clinic, five full-term babies weighing between six and eight pounds have also registered there. Of special interest is the child with spastic quadriplegia, since the nursery period was relatively uneventful, and, with a weight of 3 pounds 5 ounces, there was no particular evidence that she would become thus severely handicapped.

Two of the mothers had history of previous unsuccessful pregnancies. In one case there was a history of premature separation of the placenta and, in another, ruptured membranes for ten days.

The factor of multiple births appeared very frequently in all the data on handicapped survivors in the present series. Even one of a surviving twin set has been found fairly often to be moderately to severely handicapped, as compared with the other twin. One child in the cerebral palsy group with spasticity, microcephaly and retardation was delivered with a macerated twin fetus. In the entire series of premature infants, there were six instances in which such delivery had occurred. In three of these cases the surviving twin died shortly after birth. In one set the macerated fetus and the one born alive both had multiple anomalies. In another, the born-alive infant was edematous, breathed poorly, and died shortly after delivery. At autopsy hemorrhagic pneumonia was noted. In the third case, the mother had chronic nephritis. One twin was a macerated fetus, and the other died shortly after delivery with a meningocele and hydrocephalus. In three instances, the surviving twin was dismissed in good condition.

A follow-up of two of the babies born with a macerated twin was obtained. In one instance, the mother had toxemia. The macerated fetus was a female weighing 2 pounds 4 ounces, and the other child, a boy, weighing 5 pounds 9 ounces, was dismissed after the average hospital stay and at one year of age was normal in development. In this case, one cord was found to be obstructed. In the second case in which follow-up was obtained, a female weighing 2 pounds 8 ounces was born macerated; the twin, a male weighing 6 pounds 7 ounces, was dismissed and at five years of age was a normal, healthy child. The placenta showed degenerative change in the smaller section, and autolysis of the cord was noted. In the third case both twins were females. One, weighing 4 pounds 12 ounces, was macerated, and the other, weighing 6 pounds 6 ounces, was dismissed from the nursery appearing normal. One cord had a velamentous insertion. Follow-up data in this case could not be obtained.

When these cases were discussed at medical rounds, the statement was made that, in animals, a litter born with a macerated fetus was often considered a poor litter and the entire group was de-

stroyed. This statement was confirmed by Dr. K. F. Meyer, of Hooper Foundation, University of California, as still being the prevailing philosophy in animal husbandry. However, surviving twins in the larger animals are known to have developed normally.

A curious incident occurred in the nursery during the five-year period here reported upon. The smallest premature infant in the series whose weight dropped from 2 pounds 2 ounces to 1 pound 10 ounces, or under 1,000 grams, but whose progress was satisfactory, had an unexplained convulsion at five weeks of age, after which he showed weakness of the right arm and leg. A few days later, another premature infant in the same nursery appeared more listless than usual, ate poorly, and later it was noted that her right arm was favored. Another infant, weighing 5 pounds 8 ounces, in the nursery with these two infants, was dismissed in good condition. Later, he was brought back to the pediatric ward for circumcision and, following the operation, paralysis of both lower extremities developed. Viral studies, both by chick embryo inoculation and blood agglutination, carefully pursued, were fruitless. Two of the children, the hemiplegic and the paraplegic, were still under observation at the time this report was prepared and showed rather pronounced weakness, more of the lower motor neuron than the spastic type. The third child recovered, except for slight contracture at the right elbow. There was no history of any illness among the personnel entering the nursery. The possibility of a coxsackie virus producing the condition was considered, but proof could not be demonstrated. Two of these cases are listed in the severely handicapped group and were mentioned earlier as possibly due to infection.

The weight curves of the prematures illustrate that, even with many private pediatricians in attendance and a variety of formulae used, the gains are very similar. A special analysis of the use of breast milk will be made later. Although most of the infants were fed by bottle, a specially modified polyethylene tube used by one of the authors has proven safe, nonirritating, and especially useful for the small infants or other poor feeders. Vitamin C is given routinely, singly or in combination with other vitamins. Iron, alone, was administered to 32 infants. Twenty-two infants had transfusions only. Eight had transfusion and iron by os.

RECOMMENDATIONS

From the foregoing, it is apparent that certain information already available can be put into more general practice and that in some areas further study is needed.

1. The present knowledge of retrolental fibroplasia, even though incomplete, indicates that high concentrations of oxygen may be toxic to the visual organ, at least in certain circumstances. Oxygen should be given to premature infants under prescribed conditions.
2. Failure to establish adequate pulmonary ventilation is the most frequent cause of neonatal deaths. Knowledge of respiratory physiology is still incomplete, but the use of sedatives and anesthesia should be very carefully studied. Other means of relaxation and reassurance should be explored. Methods of resuscitation should be reviewed once or twice a year to familiarize new members of a hospital staff with good practices.
3. The method of delivery should be carefully selected and its advantages weighed against its hazards. Cesarean section, in the case of prematurity, is accompanied by such a high mortality that another choice can scarcely give a higher death rate.
4. A poor fertility history in many mothers is obvious, and this is a field that should be continually studied, not only by obstetricians, but by internists, geneticists and psychologists.
5. Multiple births obviously are statistically associated with premature mortality and morbidity, and, although by its very nature this factor is largely beyond control, there are still areas that can be further studied.
6. Although the feeding of premature babies has been simplified and much new information concerning homeostasis in the newborn is available, there is still a tendency to overhydrate and overmedicate premature infants.
7. The single most valuable educational situation is a routine review of all fatal cases, neonatal deaths, and stillbirths. Obstetricians, pediatricians, pathologists, nurses, and probably sometimes hospital administrators, should participate in such reviews. Internists, psychiatrists and geneticists should be invited when certain types of cases are discussed.
8. The standards approved by the American Academy of Pediatrics should be known in every nursery and applied in so far as possible in the local situation.

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